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Epidural versus intramuscular pethidine in postoperative pain relief

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Summary

Twenty-one patients received epidural pethidine 0,75 mg/kg in 10 ml normal saline for postoperative analgesia. A control group of 20 patients received intramuscular pethidine 1,5 mg/kg. Respiratory and cardiovascular parameters in both groups were stable, and in both side-effects were similar and not serious. In the epidural group analgesia was more intense and of longer duration and the level of consciousness was better. Central depression was present in both groups but less so in the epidural group.

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Epidural opiates are enjoying some vogue at present, their effective duration being reported as varying from several hours[1-3] in acute pain to several days in chronic pain.[4,5] The reported incidence of side-effects varies from low[2,4,6] to high.[7-9] Most reports have been on morphine, but obtaining preservative-free solutions and avoiding respiratory depression[4,5,10] are problems.

Pethidine hydrochloride was chosen for this trial because it is supplied as a preservative-free drug. Cousins *et al.*[1] and Scott and McClure[11] reported good analgesia using epidural pethidine. The site of action is thought to be the substantia gelatinosa of the spinal cord, as with other opiates.[3,5,6,12]

The aim of the study was to determine the effectiveness and duration of pain relief with epidural pethidine in the postoperative period, and the side-effects, including cardiovascular instability, respiratory instability, change in consciousness, nausea, itching and sensory disturbance. A control group of patients received intramuscular pethidine.

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Methods

The study was approved by the Tygerberg Hospital Ethical Committee, and all patients gave informed written consent. Gynaecological and orthopaedic patients were chosen because their operations were suitable for epidural anaesthesia.

Patients were allocated to the epidural group or the intramuscular group purely on an alternate basis on the pre-operative ward round. At this time the patient's resting blood pressure and pulse rate were noted. The tidal volume, respiratory rate and partial arterial oxygen (Pa_{O_2}) and carbon dioxide (Pa_{CO_2}) pressures were measured. Blood samples were taken into 2 ml heparinized glass syringes by radial artery puncture, and if there was any difficulty in obtaining arterial blood this investigation was abandoned. The blood was packed on ice and immediately taken to the laboratory for analysis. All analyses were made with the same machine, a Radiometer ABL1 blood gas analyser, using a standard technique. The tidal volumes were measured by a Wright's respirometer with patients breathing through a cardboard mouthpiece of standard lung function test size. The same Wright respirometer was used throughout; it consistently read -10% on testing.

Patients were told that postoperative analgesia would be given whenever they felt the need for it. The assessment of their pain would be left entirely up to them and they would receive analgesia whenever they became uncomfortable, i.e. on request. Patients were asked to grade their postoperative pain according to the following scale: 1 — poor; continuous, unacceptable pain; 2 —moderate; continuous, acceptable pain; 3 — good; pain present intermittently but not worrying patient; 4 — total; no pain. All pain assessments were therefore subjective. The day after the operation the patients were asked to comment on and grade the postoperative analgesia.

Standard premedication of pethidine 0,75 mg/kg and promethazine 0,35 mg/kg was given intramuscularly 1 hour preoperatively. In patients in both groups an epidural catheter was then inserted at L2-3 or L3-4. Lignocaine 1,5% with adrenaline was used because of its short action, and the operation was

performed under epidural block only when possible. When this was insufficient because of surgical technique or if the patient wished to be asleep, standard general anaesthesia with intravenous thiopentone induction and maintenance with nitrous oxide, oxygen, halothane 0,5% and alcuronium was added. Neostigmine and atropine were given to reverse the effects of alcuronium. In all cases the epidural block was effective (see Table I).

Postoperatively patients were kept under close observation for 24 hours. Analgesia was with preservative-free pethidine; patients in the intramuscular group received 1,5 mg/kg and those in the epidural group 0,75 mg/kg in 10 ml normal saline via an epidural catheter with a 2 μm filter. The epidural dose was arbitrarily chosen because a preliminary study had shown 0,25 mg/kg to be inadequate.

After 1 hour and 4 hours the following were noted: level of consciousness (graded as follows: 1 — fully awake; 2 — drowsy; 3 — sleeping but rousable; 4 — stuporous); heart rate; blood pressure; blood gas levels; and respiratory rate and volume. Arterial blood samples were drawn into heparinized 2 ml glass syringes, packed in ice and sent for immediate analysis. Doubtful arterial samples were discarded.

Patients were specifically questioned about nausea and asked to grade it on the following scale: 1 — none; 2 —mild, no anti-emetic; 3 — moderate, requires anti-emetic; 4 — severe, present despite anti-emetic. Metoclopramide was used as an anti-emetic. Skin sensation to pinprick, light touch, heat and cold was tested in the trunk and lower limbs, as was proprioception.

Results

Groups (Table I)

There were 20 patients in the intramuscular group and 21 in the epidural group (in patient 13 no postoperative parameters were measured). Details regarding sex, age, and weight of the patients in the two groups are given in Table I. The epidural group had a higher American Society of Anesthetists (ASA) grading (mean 1,66) than the intramuscular group (mean 1,35).

Analgesia (Tables II and III)

Analgesia was of longer duration and of better quality in the epidural group (Table III). The first epidural dose was effective for 1,26 hours longer than the intramuscular analgesia and the second dose for 0,45 hour longer. These differences are not statistically significant ($P > 0,05$). Some patients experienced remarkable relief; for example, patient 13 had pain relief lasting 48 hours following the first dose after major surgery, patient 7 had no pain after the first dose, and patients 1, 2, 5, 6 and 17 had no pain after the second dose. This was a very significant and positive finding. In the intramuscular group only patient 1 required no further analgesia after the first dose, which, however, precipitated respiratory arrest requiring ventilation for 1 hour and then naloxone 0,8 mg intravenously. The patient then awoke and breathed well.

The degree of analgesia was markedly better in the epidural group, frequently being described by the patient as grade 4 or total analgesia. Only patient 19 had poor pain relief, which remained poor when intramuscular pethidine was substituted after the third epidural pethidine dose. The majority of the patients in the intramuscular group had good analgesia of grade 3 level (pain still present but not obtrusive). Only 3 out of 20 had total pain relief compared with 15 out of 21 in the epidural group. The mean analgesia score in the epidural group was 3,52 and that in the intramuscular group 2,65. At a confidence level of 95% this difference is significant ($P < 0,05$). Epidural pethidine provided a shorter duration of analgesia in patients who had undergone

TABLE I. THE PATIENTS

Intramuscular group*			Epidural group†		
Patient No.	Operation	Anaesthetic	Patient No.	Operation	Anaesthetic
1	AH	GA‡	1	VH	Epidural
2	AH	GA	2	Salpingostomy	Epidural + GA
3	AH	GA	3	AH	Epidural + GA
4	VH	Epidural	4	VH	Epidural
5	VH	Epidural	5	AH	Epidural + GA
6	VH	Epidural	6	AH	Epidural + GA
7	AH	GA	7	Laparoscopy	Epidural
8	AH	GA	8	VH	Epidural
9	AH	GA	9	AH	Epidural + GA
10	AH	GA	10	VH	Epidural
11	AH	GA	11	AH	Epidural + GA
12	AH	GA	12	VH	Epidural
13	Laparoscopy	GA	13	Total cystectomy	Epidural + GA
14	Femur osteotomy + plate	GA	14	Fusion right knee	Epidural
15	Plate for fractured femur	Epidural	15	Meniscectomy knee	Epidural
16	Bilateral knee internal ligament repair	Epidural	16	Fusion right knee	Epidural
17	Operation knee	Epidural	17	Osteotomy tibia	Epidural + GA
18	Osteotomy + plate left femur	Epidural	18	Plate for fractured femur	Epidural
19	Plate for fractured femur	GA	19	Bilateral internal knee ligament repair	Epidural
20	Excision head of radius	GA	20	Moore's prosthesis	Epidural
			21	Meniscectomy	Epidural

*There were 15 females and 5 males in the group; the mean age was 42,6 yrs, the mean weight 69 kg and the mean ASA rating 1,35.
†There were 16 females and 5 males in the group; the mean age was 44,9 yrs, the mean weight 64,8 kg and the mean ASA rating 1,66.
‡Patients receiving GA all also received epidural anaesthesia.
AH = abdominal hysterectomy; VH = vaginal hysterectomy; GA = general anaesthesia.

TABLE II. ANALGESIA, NAUSEA AND LEVEL OF CONSCIOUSNESS IN THE INTRAMUSCULAR GROUP

Patient No.	Age (yrs)	Sex	Duration of analgesia (h)			Analgesia (grade 1-4)	Nausea (grade 1-4)	Level of consciousness (grade 1-4)	
			1st dose	2nd dose	3rd dose			1 h	4 h
1*	55	F	No pain after first dose			4	1	4	2
2	30	F	3	3,5	4	2	1	1	1
3	45	F	12	5	6	3	4	4	3
4	53	F	3,25	6	4	3	2	2	1
5	72	F	11	8	8	3	2	3	2
6	68	F	1	4	6	3	1	3	2
7	27	F	3	7	5	3	1	3	1
8	46	F	7	5,25	7	3	3	2	2
9	47	F	6	6	8	3	1	2	1
10	43	F	4	4	7	3	4	3	3
11	45	F	6,75	4	8	2	1	3	1
12	50	F	6,5	10	10	2	1	3	2
13	25	F	4,5	5	9,5	3	2	2	2
14	54	F	3	5	11	3	1	2	1
15	25	M	4	5,5	7,5	2	1	3	3
16	30	M	1	1	2	1	1	1	1
17	34	M	8,5	5	5	4	1	1	1
18	16	M	6,5	10	10	4	1	2	1
19	24	M	1	3	5	1	1	2	1
20	63	F	4	7	13	1	1	2	1
Mean	**42,6**		**5,05 + 1 infinity**	**5,48**	**7,15**	**2,65**	**1,55**	**2,40**	**1,55**

*Patient 1 was given intermittent positive-pressure ventilation for respiratory arrest. After 1 h she was not breathing and stuporous. Naloxone 0,8 mg intravenously resulted in waking and spontaneous respiration but no pain.

orthopaedic procedures than in those who had undergone gynaecological procedures. This was not apparent in the patients who received the drug intramuscularly.

The onset of analgesia was rapid in the epidural group, analgesia being evident at 5 minutes and very good by 10 minutes. The intramuscular analgesia took 15 minutes to have some effect and 30 minutes to be effective. Very noticeable was the clean endpoint of analgesia in the epidural group over a short period of 10-15 minutes; pain relief in the intramuscular group, never as profound, wore off more slowly.

In the epidural group patient 16 received naloxone 0,4 mg intravenously after developing respiratory depression, but this did not affect the analgesia. Thereafter patients 17 and 18 also received naloxone 0,4 mg intravenously after their 1-hour respiratory, blood gas and other parameters had been measured. This caused a lightening of consciousness but not to changes in analgesia. These 2 patients received naloxone purely to study the effect on analgesia.

Level of consciousness (Tables II and III)

The level of consciousness on a 1-4 grading was less depressed in the epidural group at 1 hour, the mean score being 1,71 as opposed to 2,40 in the intramuscular group. This difference was statistically significant at a 95% confidence level ($P < 0,05$). At 4 hours differences were not significant.

Members of the epidural group were generally more actively interested in what went on around them. However, patients 1, 8, 12, 18 and 20 showed a sudden onset of drowsiness 5 minutes after administration, progressing to light sleep without measurable respiratory or cardiovascular depression. This lasted for 20 minutes, after which they returned to the previous level of consciousness.

Nausea and side-effects (Tables II and III)

Nausea was not severe, the intramuscular group scoring 1,55 and the epidural group 1,38 on the 1-4 scale. Of the intramuscular group, 6 (30%) experienced nausea as against 5 (24%) of the epidural group. Itching did not occur in either group, nor was skin sensation, proprioception or motor function changed. One patient in the epidural group complained of lameness in the legs, but examination revealed no abnormality. No urinary retention occurred.

Respiratory function

Changes in respiration were not marked. Mean blood gas changes at 1 hour were as follows: Pa_{O_2} -0,6 kPa in the intramuscular group and -1,15 kPa in the epidural group (-0,85 kPa if patient 16 is excluded); Pa_{CO_2} +0,53 kPa in the intramuscular group and +0,48 kPa in the epidural group (+0,42 kPa if patient 16 is excluded). At 4 hours the mean changes were: Pa_{O_2} -0,30 kPa in the intramuscular group and -0,97 kPa in the epidural group; Pa_{CO_2} +0,26 kPa in the intramuscular group and +0,11 kPa in the epidural group. Patient 1 in the intramuscular group and patient 13 in the epidural group are not included in these calculations. The mean minute volume changes were minimal at 1 and 4 hours. However, the range is very great, as many of the patients actively hyperventilated when the respirometer was brought near them.

Respiratory depression was evident in 1 patient in the epidural group (No. 16) at 1 hour. Her minute volume fell by 49%, her Pa_{O_2} fell by 5,3 kPa and her Pa_{CO_2} rose by 1,2 kPa. She responded rapidly to intravenous naloxone 0,4 mg. As already noted, patient 1 in the intramuscular group developed respiratory arrest 10 minutes after her first dose of analgesia. Her 1-hour parameters are not included in the calculations.

Cardiovascular system

Cardiovascular stability was a feature in both groups. Mean changes in blood pressure at 1 and 4 hours were similar in both

TABLE III. ANALGESIA, NAUSEA AND LEVEL OF CONSCIOUSNESS IN THE EPIDURAL GROUP

Patient No.	Age (yrs)	Sex	Duration of analgesia (h) 1st dose	2nd dose	3rd dose	Analgesia (grade 1-4)	Nausea (grade 1-4)	Level of consciousness (grade 1-4) 1 h	4 h
1	72	F	11,25	8	None	4	2	3	3
2	28	F	10	14	None	4	1	3	1
3	20	F	6	10	9	4	1	2	2
4	38	F	6	8	8	3	1	2	1
5	34	F	5,5	8	None	3	1	2	1
6	40	F	6	15	None	3	1	1	1
7	29	F	No pain after first dose			4	1	2	2
8	48	F	8	9	16	4	1	3	1
9	39	F	5,75	4	7,5	2	1	1	1
10	48	F	5,25	3,5	4	4	1	1	1
11	31	F	4,25	7	7	4	3	1	1
12	28	F	2	3	6	3	1	1	1
13	52	M	No pain for 48 h then mild pain			3	2	1	1
14	53	F	2	2	4	4	4	2	1
15	22	M	4,5	2	5	4	2	1	1
16*	65	F	2,5	5,5	4	4	1	2	1
17†	66	F	12,5	10	None	4	1	1	1
18†	56	M	6	2,5	6	4	1	2	1
19	50	M	2,25	1,5	4	1	1	2	1
20	20	F	16	None after second dose		4	1	1	1
21	41	M	4,25	3	6	4	1	2	3
Mean	44,9		6,31 + 2 infinity	6,33 + 1 infinity	6,19 + 5 infinity	3,52	1,38	1,71	1,28

*Patient 16 was given naloxone 0.4 mg intravenously at 1 h for respiratory depression. Analgesia was not reversed although the patient woke up fully and breathed well.
†Patients 17 and 18 were given naloxone 0.4 mg intravenously at 1 h to test analgesic response.

groups, the systolic pressure falling more in the epidural group at 1 hour (8,8%) and at 4 hours (6,8%). Diastolic changes were minimal, as were heart rate changes and pulse changes. The ranges of blood pressure and heart rate changes were greater in the intramuscular group. Despite this, with regard to blood pressure and perfusion no patient's condition caused anxiety.

Discussion

Much information has been published on the effectiveness[1,2,9,13] and problems of epidural morphine, particularly respiratory depression[9,10] and pruritus.[7,8] In a comparison with intramuscular morphine the epidural route proved superior.[6] Since epidural morphine is not recommended[8,9] for routine use, a safe alternative would be useful.

In this study epidural pethidine provided analgesia of better quality than intramuscular pethidine, but analgesia was not of significantly longer duration ($P > 0,05$) in those patients who required repeated analgesia. All the patients in the intramuscular group needed repeated analgesia, on average at 6-hourly intervals, but of those in the epidural group 8 out of 21 needed no further analgesia after their first or second dose. The variation in duration of pain relief in the epidural group was very wide, from 2 hours to infinity for the first dose. This wide variation in duration has been shown in other studies on epidural opiates.[1,4,5,14] Possible causes are different pain thresholds, varying rates of absorption into CSF or blood and different sites of injection in different studies.[13,15,16] Here the pethidine was injected via the catheter already used for surgical analgesia, so that no doubt existed as to correct location. In only 1 patient in the epidural group was analgesia poor. This appeared to be due to failure to respond to the drug, since intramuscular pethidine was equally ineffective.

Many pain studies have attempted to grade pain objectively to enable trained observers to determine the level of pain[17] and the need for analgesia. However, it was felt that only the patients themselves could decide how much pain they experienced and whether they required analgesia. This approach is supported by Wilson and Yaksh[18] and others.[13,19]

This makes evaluation of the degree of analgesia subjective, and statistical comparison becomes difficult. The patients in the epidural group experienced a better grade of analgesia with fewer central effects. The ideal of complete analgesia without disturbance of normal sensation was achieved in 15 out of 21 patients. This was not matched by the intramuscular route — here central effects, causing diminished emotional response to pain,[20] cover the less effective analgesia.

The rapid onset of epidural opiate analgesia was noted, as in other studies.[1,4,5] Analgesia became evident within 5 minutes and pain was absent by 10 minutes. The patients then remained pain-free until pain returned rapidly over 10-15 minutes. The fact that the patients in the epidural group were more fully awake may indicate that they became aware of pain at a lower threshold than those in the intramuscular group.

An interesting phenomenon was seen in 5 patients in the epidural group. Five minutes after the administration of pethidine they suddenly became drowsy, this coinciding with the onset of analgesia. There was no apparent cardiovascular or respiratory depression. This lasted for 20 minutes, after which they spontaneously awoke. This indicates that the opiate initially reaches the brain but that its action persists in the spinal cord.

The onset of analgesia and drowsiness at this time matches the rapid rise in cerebrospinal fluid (CSF) pethidine levels following epidural administration shown by Cousins *et al.*[1] Since CSF circulation[21] is in a downward direction, some other mechanism must cause the rapid effect on the higher brain areas.

The improved level of consciousness in the epidural group is significant at a confidence level of 95% ($P < 0,05$). This allows effective physiotherapy and early mobilization, as previously noted.[1,6,13,16] The patients in the epidural group were very positive about the pain relief and adequacy of their analgesia. Those

in the intramuscular group were hazy in their recollections of the immediate postoperative period and commented on amnesia, discomfort and unpleasant injections.

Respiration was stable in both groups, apart from 1 patient from each group who showed definite depression. Minute volume measurements were of little value, blood gas levels being more reliable in the less fit and active patient. The epidural group showed a consistent mild fall in Pa_{O_2} and a consistent mild rise in Pa_{CO_2}, more marked at 1 hour than at 4 hours but of little consequence. This would suggest a mild central depressant effect. Blood gas changes were very similar in the intramuscular group.

There are many reports of dangerous respiratory depression after epidural morphine[9,10] and pethidine.[11] Of these 21 patients only 1, No. 16, had respiratory depression at an early stage, 1 hour after epidural pethidine. The patients were closely watched for 24 hours, but no other respiratory depression occurred. Nevertheless, potential respiratory failure in 1 out of 20 patients makes the technique unsuitable for routine ward use.

This patient demonstrated a previously reported phenomenon.[11,22] She was given naloxone 0,4 mg intravenously with rapid and sustained reversal of the level of consciousness and respiratory depression, analgesia being unaffected. The next 2 patients had no signs of depression at 1 hour, but after their 1-hour parameters were measured they were also given naloxone 0,4 mg intravenously with no change in the level of analgesia. This is a major advantage over parenteral opiates. Why this resistance to naloxone reversal of analgesia should be present is unclear. Patient 1 in the intramuscular group developed respiratory arrest, requiring ventilation for 1 hour followed by naloxone. This would indicate that intramuscular pethidine is as unsafe as epidural pethidine, yet over years of use intramuscular pethidine has been recognized as safe, so epidural pethidine cannot be condemned on the basis of 1 out of 21 cases either, and further studies are indicated.

Cardiovascular stability has been noted in many epidural opiate trials.[2,6,14] The slight difference between systolic blood pressures in the two groups found here is easily explained by the better analgesia achieved with epidural pethidine. The diastolic blood pressures were very similar.

The incidence of nausea, 30% in the intramuscular group and 24% in the epidural group, was not significantly different. This compares with other studies on postoperative nausea.[19] Epidural pethidine does not increase the incidence of nausea.

Pethidine has a strong local anaesthetic action,[23] but as in other studies on epidural opiates[1,2,13,14] no disturbance of sensation, proprioceptive, autonomic or motor function could be demonstrated. Retention of urine has been described with morphine[13] but was not seen in any of the patients in this study. Pruritus is another problem associated with morphine and is often very severe,[7,8] but no patient in this study experienced it.

Conclusion

Epidural pethidine 0,75 mg/kg in 10 ml normal saline provides effective analgesia without cardiovascular instability and with minimal alteration in levels of consciousness. This allows effective physiotherapy and early mobilization.

The method has advantages over the intramuscular route and offers better cardiovascular stability than regional analgesia, without sensory disturbance. The possibility of respiratory depression must be borne in mind. This, with the early drowsiness and the 25% incidence of nausea, indicates that some opiate is reaching the brain, either via the CSF or blood.

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